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Original Research

Use of cystatin C to inform metformin eligibility among adult veterans with diabetes

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ABSTRACT

Aims: Recommendations for metformin use are dependent on eGFR category: eGFR >45 ml/min/1.73 m² – "first-line agent"; eGFR 30–44 – "use with caution"; eGFR<30 – "do not use". Misclassification of metformin eligibility by creatinine-based MDRD GFR estimates (eGFRcr) may contribute to its misuse. We investigated the impact of cystatin c estimates of GFR (eGFRcys) on metformin eligibility.
Methods: In a consecutive cohort of 550 Veterans with diabetes, metformin use and eligibility were assessed by eGFR category, using eGFRcr and eGFRcys. Discrepancy in eligibility was defined as cases where eGFRcr and eGFRcys categories (<30, 30–44, 45–60, and >60 ml/min/1.73 m²) differed with an absolute difference in eGFR of >5 ml/min/1.73 m². We modeled predictors of metformin use and eGFR category discrepancy with multivariable relative risk regression and multinomial logistic regression.
Results: Subjects were 95% male, median age 68, and racially diverse (45% White, 22% Black, 11% Asian, 22% unknown). Metformin use decreased with severity of eGFRcr category, from 63% in eGFRcr >60 to 3% in eGFRcr <30. eGFRcys reclassified 20% of Veterans into different eGFR categories. Factors associated with a more severe eGFRcys category compared to eGFRcr were older age (aOR = 2.21 per decade, 1.44–1.82), higher BMI (aOR = 1.04 per kg/m², 1.01–1.08) and albuminuria >30 mg/g (aOR = 1.81, 1.20–2.73).
Conclusions: Metformin use is low among Veterans with CKD. eGFRcys may serve as a confirmatory estimate of kidney function to allow safe use of metformin among patients with CKD, particularly among older individuals and those with albuminuria.

Introduction

Goals of Healthy People 2020 include developing strategies for safe and effective glycemic control [1]. One key strategy to attain this goal is to promote greater use of metformin. Compared to other oral hypoglycemic agents, metformin is associated with decreased risk of cardiovascular events, slower progression of chronic kidney disease (CKD) and lower death rates [2,3]. Also, metformin does not induce hypoglycemia, a common and potentially very serious adverse side effect of insulin secretagogues, such as sulfonylureas [4].

Because metformin is renally cleared, individuals with severely reduced kidney function who use metformin may be at risk of lactic acidosis [4,5]. Since its introduction to the US market, metformin has thus been labeled with a black box warning contraindicating its use among men with a serum creatinine of ≥1.5 mg/dL and women with a serum creatinine of ≥1.4 mg/dL. As the benefits of metformin have become more widely appreciated, there has been an ongoing debate as to whether these serum creatinine thresholds are too restrictive and whether estimated glomerular filtration rate (eGFR) is a more accurate estimation of kidney function and thus metformin eligibility [6]. The United Kingdom National Institute for Health and Clinical Excellence (NICE) and Kidney Disease Improving Global Outcomes specifically recommend use of metformin for individuals with an estimated glomerular filtration rate (eGFR) of ≥45 ml/min/1.73 m², review and cautious use of lower doses of metformin for individuals with an eGFR of 30–44 ml/min/1.73 m², and not to use metformin for individuals with an eGFR of <30 ml/min/1.73 m² [7,8]. In a 2012 joint position statement, the American Diabetes Association and European Association for the Study of Diabetes concluded that these guidelines appeared very reasonable [9].

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However, metformin is underused among individuals with diabetes and CKD [10]. This is likely multifactorial, including conflicting messages between the FDA and the aforementioned professional societies [10–12]. Clinician concerns about misclassification of kidney function by eGFRcr may also be contributing. The aforementioned recommendations are based upon creatinine estimates of kidney function (eGFRcr), which are influenced by age, gender, ethnicity, and muscle mass. Importantly, these equations do not include muscle mass per se, but use age, gender, and ethnicity to estimate it. Use of creatinine-based estimates of kidney function may thus lead to biases in GFR estimation across and within individuals [13].

Cystatin C estimates of kidney function (eGFRcys) appear to be more accurate than eGFRcr in older, unselected adults, and they have been more strongly associated with health outcomes across numerous research cohorts [14]. eGFRcys is independent of muscle mass [15]. National and international CKD guidelines now recommend the use of cystatin C to confirm eGFR among individuals for whom eGFRcr may be unreliable [16], such as in older, frail adults among whom creatinine generation due to loss of muscle mass may decrease in parallel with GFR decline, effectively masking the actual loss of GFR [17]. This is also of concern for diabetic adults, in whom skeletal muscle mass is also reduced relative to total body mass [18,19].

Our objectives in this study were: 1) to examine independent predictors of metformin use; 2) to compare categorization of kidney function based upon eGFRcys versus MDRD eGFRcr to determine metformin eligibility among adults with diabetes; 3) to identify characteristics associated with different eGFR categories by cystatin C and creatinine.

Subjects, materials and methods

Study design and study participants

This was a cross-sectional study using data from a cohort of adult Veterans with diabetes who were receiving primary care at the San Francisco Veterans Administration Medical Center (SFVAMC). Veterans were eligible for this study if they were included in the local Medical Practice Performance Measures Dashboard, a local diabetes registry designed to improve the quality of diabetes care delivered to adult Veterans, and if they received their medications from the SFVAMC pharmacy. The first 550 patients who met these criteria were included in this study. The study protocol was approved by the Committee of Human Research at the SFVAMC and University of California, San Francisco.

Data collection

Participant demographic information (age, gender, race/ethnicity), body-mass index (BMI), co-morbid conditions from the problem list (hypertension, cardiovascular disease, congestive heart failure), diabetes medication use (metformin, sulfonylurea, insulin, thiazolidinedione), and laboratory data (glycosylated hemoglobin, urinary albumin-to-creatinine ratio, serum creatinine, MDRD eGFRcr) were ascertained by chart review between November 2013 and March 2014. Only data updated in the prior three months were abstracted. Serum creatinine and MDRD eGFR measures were obtained for clinical purposes and were available to clinicians. CKD-EPI eGFRcr and cystatin C were obtained only for research purposes and were not available to clinicians. The creatinine assay was IDMS standardized. Cystatin C measures were performed on a Beckman Synchron DX600 analyzer with reagents produced by Gentian (Norway) and distributed by Beckman. Intra-assay coefficients of variation for cystatin C, estimating within-run precision, ranged from 0.80 to 1.71% with mean serum concentrations between 0.96 and 2.95 mg/L. Inter-assay coefficients of variation for cystatin C, estimating day-to-day precision, ranged from 2.76 to 3.37% with mean serum concentrations between 1.01 and 3.93 mg/L.

Definitions

Metformin eligibility by clinical eGFR category was defined using the most recent recommendations [6,9]: first line agent if eGFR >60 ml/min1/.73 m^2; first line agent if eGFR 45–60 ml/min/1.73 m^2; use with caution if eGFR 30–44 ml/min/1.73 m^2; do not use if eGFR <30 ml/min/1.73 m^2. Discrepancy between eGFRcys and MDRD eGFRcr was defined as cases where clinical eGFR categories differed by GFR estimate and the eGFR values were at least 5 ml/min/1.73 m^2 apart.

Covariates

Candidate covariates included demographic characteristics (age, gender, race/ethnicity), co-morbid conditions (hypertension, hyperlipidemia, cardiovascular disease, congestive heart failure), BMI, treatment of diabetes using glycosylated hemoglobin and urine albumin-to-creatinine ratio (ACR). We examined the relationship of continuous parameters including age, BMI, glycosylated hemoglobin and ACR using smoothing splines to determine whether associations with outcomes were linear [20]. In the final models, we dichotomized glycosylated hemoglobin (≥7%, ≥5.30 mmol/mol) and ACR (>30 mg/g). Multiple imputation with the Markov chain Monte Carlo method was used to impute missing covariates, with 10 imputations to yield ~95% relative efficiency [21].

Statistical methods

Participant characteristics and diabetic medication use were compared by eGFR category using the Kruskal–Wallis test for continuous parameters and χ^2 tests for categorical parameters. Multivariable relative risk regression with a robust variance estimator and a Poisson working model was used to identify predictors of metformin use [22]. We used stepwise backward selection with a significance level of $\alpha = 0.05$ to remove candidate covariates that were not associated with the outcome. In addition to the candidate covariates listed above, either eGFRcr or serum creatinine was included in the models for metformin use. Reclassification of metformin eligibility by eGFR estimating equation was also performed across the clinical eGFR categories. We calculated the number-needed-to-screen (NNS) by cystatin C to identify a patient with an eGFR of <30 ml/min/1.73 m^2, as this person would not be eligible for metformin. Multinomial logistic regression was used to identify factors associated with bidirectional discrepancy between eGFRcys and eGFRcr categories using agreement between methods ("same category") as the reference group. Sensitivity analyses were performed using eGFRcr defined by CKD-EPIcr [23] to broaden generalizability of study results to institutions that use CKD-EPIcr estimates of GFR for clinical purposes. All analyses were conducted using the SAS system, version 9.3 (SAS Institute, Inc., Cary, NC).

Results

Characteristics of the study population

Overall, the 550 cohort subjects were 95% male, of diverse racial/ethnic backgrounds (45% White, 22% Black, 11% Asian, 22% unknown), and had a median age of 68 years. The median MDRD eGFRcr, CKD-EPI eGFRcr and eGFRcys were 73 ml/min/1.73 m^2, 69 ml/min/1.73 m^2, and 59 ml/min/1.73 m^2, respectively. Characteristics included in our analysis are summarized in Table 1, stratified by

Table 1
Characteristics of SFVA adult veterans with diabetes, by MDRD eGFRcr category

Parameter	eGFR MDRD <30 ml/min/1.73 m^2 (n = 31)	eGFR MDRD 30–44 ml/min/1.73 m^2 (n = 58)	eGFR MDRD 45–60 ml/min/1.73 m^2 (n = 93)	eGFR MDRD >60 ml/min/1.73 m^2 (n = 368)	P-value
Male	30 (97%)	55 (95%)	87 (94%)	350 (95%)	0.89
Age (y)	69 (65–78)	78 (70–84)	75 (66–82)	66 (61–74)	<0.0001
20–39	0	0	0	2 (1%)	
40–59	3 (10%)	1 (2%)	9 (10%)	76 (21%)	
60–79	22 (71%)	34 (59%)	55 (59%)	245 (67%)	
≥80	6 (19%)	23 (40%)	29 (31%)	45 (12%)	
Race/ethnicity					0.06
African-American	11 (35%)	8 (14%)	19 (20%)	81 (22%)	
Asian/Pacific Islander	4 (13%)	7 (12%)	15 (16%)	37 (10%)	
White	7 (23%)	31 (53%)	39 (42%)	171 (46%)	
Unknown	9 (29%)	12 (21%)	20 (22%)	79 (21%)	
Hypertension	30 (97%)	53 (91%)	82 (88%)	283 (77%)	0.0009
Hemoglobin A1c	7.1 (5.9–8.4)	7.2 (6.5–8.1)	7.0 (6.3–7.5)	6.9 (6.2–7.9)	0.42
<7% (<53 mmol/mol)	14 (45%)	23 (40%)	46 (49%)	198 (54%)	
7–7.9% (53–63 mmol/mol)	7 (23%)	19 (33%)	31 (33%)	81 (22%)	
8–8.9% (64–74 mmol/mol)	6 (19%)	6 (10%)	7 (8%)	40 (11%)	
≥9% (>75 mmol/mol)	4 (13%)	10 (17%)	9 (10%)	49 (13%)	
BMI (kg/m^2)	31 (25–34)	29 (26–33)	28 (25–32)	31 (27–35)	0.02
Hyperlipidemia	22 (71%)	40 (69%)	66 (71%)	260 (71%)	0.99
Cardiovascular disease	8 (26%)	9 (16%)	13 (14%)	52 (14%)	0.37
Congestive heart failure	9 (29%)	22 (38%)	15 (16%)	26 (7%)	<0.0001
Creatinine (mg/dL)	3.34 (2.68–6.96)	1.88 (1.70–2.06)	1.43 (1.32–1.53)	0.96 (0.85–1.10)	<0.0001
eGFR MDRD	22 (9–26)	38 (33–41)	54 (50–57)	86 (73–100)	<0.0001
eGFRcr CKD Epi 2012	19 (9–23)	34 (29–37)	50 (45–52)	82 (69–94)	<0.0001
eGFRcys	20 (9–24)	31 (25–37)	46 (36–53)	73 (56–92)	<0.0001
ACR (mg/g)	759 (110–1616)	61 (20–319)	36 (10–149)	11 (5–40)	<0.0001

Abbreviations: eGFR = estimated glomerular filtration rate; MDRD = Modified Diet in Renal Disease; BMI = body mass index.
Continuous outcomes are summarized by median (interquartile range).

eGFRcr MDRD category. Participants with lower eGFRcr tended to be older, had higher rates of hypertension and congestive heart failure, and higher ACR, compared to those with higher eGFRcr (Table 1). Treatment of diabetes as measured using hemoglobin A1c was similar across eGFR categories.

Prevalence of diabetes medication use

Overall metformin use was 51% and was inversely proportional to severity of CKD, defined by eGFRcr category (Fig. 1): 63% in eGFRcr >60 ml/min/1.73 m^2, 45% in eGFRcr 45–60 ml/min/1.73 m^2, 8% in eGFRcr 30–44 ml/min/1.73 m^2, and 3% in eGFRcr <30 ml/min/1.73 m^2 ($p < 0.001$). By contrast, the prevalence of insulin use increased with more severe eGFRcr categories (from 25% in those with eGFRcr of >60 ml/min/1.73 m^2 to 65% in those with eGFRcr of <30 ml/min/1.73 m^2, $p < 0.001$). Overall sulfonylurea use was 28% and was highest among individuals with an eGFR of 45–60 ml/min/1.73 m^2. Thiazolidinedione use was low (7% overall) and did not differ by eGFRcr category ($p = 0.82$). Similar trends in prevalence of diabetes medication use were noted when severity of kidney disease was defined by serum creatinine rather than eGFRcr (data not shown).

Predictors of metformin use

In the unadjusted model examining predictors of metformin use, we found higher probability of metformin use associated with higher eGFRcr, with a plateau observed around 70–80 ml/min/1.73 m^2 ($p < 0.0001$, Supplemental Fig. S1). In multivariable analysis, kidney function defined by either eGFRcr or serum creatinine was the strongest predictor of metformin use, independent of age, gender, race, diabetes control, and congestive heart failure (Table 2 and Supplemental Table S1), though clinicians seemed to be more influenced

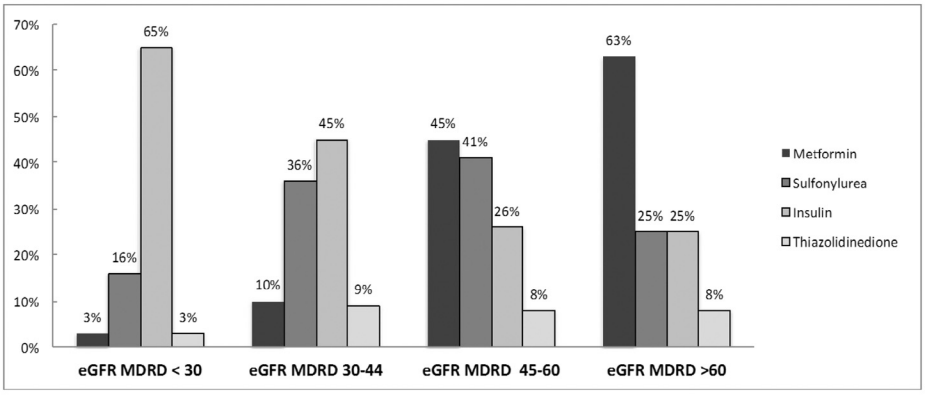

Figure 1. Diabetes medication use by adult Veterans in San Francisco, by eGFR category.

Table 2
Factors associated with metformin use among SFVA adult veterans with diabetes using MDRD (n = 550)

Parameter	Unadjusted	Adjusted
	Relative risk (95%CI)	Relative risk (95%CI)
eGFRcr <30 vs. >60	**0.05 (0.01, 0.38)**	**0.06 (0.01, 0.43)**
eGFRcr 30–44 vs. >60	**0.15 (0.07, 0.34)**	**0.18 (0.08, 0.41)**
eGFRcr 45–60 vs. >60	**0.71 (0.55, 0.93)**	**0.77 (0.59, 0.99)**
Age (per decade)	**0.83 (0.77, 0.90)**	0.93 (0.86, 1.01)
Female vs. male	1.29 (0.96, 1.72)	1.11 (0.83, 1.49)
African-American vs. Caucasian	0.90 (0.72, 1.13)	0.94 (0.77, 1.14)
Asian/other vs. Caucasian	1.19 (0.95, 1.51)	1.27 (1.04, 1.56)
Hypertension	0.87 (0.72, 1.05)	
Hyperlipidemia	1.12 (0.92, 1.35)	
BMI (per kg/m^2)	1.00 (0.99, 1.01)	
A1c <7% (5.3 mmol/mol) vs. ≥7% (≥5.3 mmol/mol)	**0.85 (0.72, 1.00)**	**0.81 (0.69, 0.94)**
ACR > 30 mg/g	**0.74 (0.61, 0.90)**	
Cardiovascular disease	0.82 (0.63, 1.07)	
Congestive heart failure	**0.40 (0.26, 0.63)**	**0.58 (0.39, 0.87)**
Insulin use	**0.79 (0.65, 0.97)**	

Abbreviations: MDRD = Modified diet in renal disease; BMI = body mass index.

Table 4
Factors associated with discrepancy[a] in eGFR category[b], among adult Veterans with diabetes (n = 550)

Parameter	eGFRcys vs. eGFR MDRD category	
	eGFRcys less severe vs. Same category Odds ratio (95%CI) n = 19	eGFRcys more severe vs. Same category Odds ratio (95%CI) n = 178
Age (per decade)	1.36 (0.76, 2.44)	**2.21 (1.79, 2.73)**
Female vs. male	2.77 (0.38, 20.40)	1.15 (0.44, 2.96)
African-American vs. Caucasian	0.32 (0.06, 1.71)	0.93 (0.54, 1.60)
Asian/other vs. Caucasian	0.40 (0.06, 2.71)	0.93 (0.48, 1.82)
BMI (per kg/m^2)	0.98 (0.88, 1.08)	**1.04 (1.01, 1.08)**
Urinary ACR > 30 mg/g	1.88 (0.56, 6.26)	**1.81 (1.20, 2.73)**

Abbreviations: ACR = albumin-to-creatinine ratio.
[a] Discrepancy between eGFRcys and eGFRcr is defined as cases where the eGFRcys category is more or less severe than eGFRcr category, and the two eGFR values differ by at least 5 points.
[b] eGFR categories are: <30, 30–45, 45–60, >60.
Bold values depict statistically significant associations.

to withhold metformin due to eGFRcr than serum creatinine. In the fully adjusted model, compared to individuals with an MDRD eGFRcr of >60 ml/min/1.37 m^2, the likelihood of metformin use was 23% lower for persons with eGFRcr of 45–59 ml/min/1.73 m^2 and 82% lower among individuals with an MDRD eGFRcr of 30–44 ml/min/1.73 m^2. In a comparable, multivariable adjusted model using serum creatinine, compared to individuals with a serum creatinine of <1.2 mg/dL, the likelihood of metformin use was 51% lower among individuals with a serum creatinine of 1.5 to < 1.8 mg/dL. Among those with a creatinine of 1.2–1.5 mg/dL, the likelihood of metformin use was 22% lower, although the association did not reach statistical significance (p = 0.23). Individuals with better controlled diabetes, defined by a glycosylated hemoglobin <7.0% (5.3 mmol/mol), and those with congestive heart failure were also less likely to be prescribed metformin, independent of other factors. Younger age appeared strongly associated with metformin use in unadjusted analysis, though results were attenuated and not statistically significant after adjustment for eGFR categories. Similar results were noted when analyses were performed using the CKD-EPI equation to calculate eGFRcr, but with a stronger age effect (Supplemental Table S2).

Reclassification of metformin eligibility by eGFRcys vs. eGFRcr

Using MDRD eGFRcr categories, 84% (95%CI, 81.0–87.0, n = 461) of individuals were eligible to use metformin as first line therapy, whereas 10.6% (95%CI, 8.0–13.1, n = 58) were eligible to use metformin with caution, and 5.6% (95%CI, 3.7–7.6, n = 31) were not eligible to use metformin. Relative to eGFRcr, eGFRcys reclassified 109 (20% of 550) patients into different eGFR categories, including 32 (5.8% of 500) patients reclassified downward into "do not use" and 70 (12.7% of 550) reclassified downward into "use with caution" (Table 3). The weighted kappa coefficient was 0.57 suggesting moderate agreement between eGFRcr and eGFRcys, while Bowker's test of symmetry was rejected (p < 0.001), suggesting a significant difference in classification. Only 7 (1.3% of 550) patients were classified upward into a less severe eGFR category. The percentages of patients who were reclassified by eGFRcys to <30 ml/min/1.73 m^2 rose from 1% (number needed to screen [NNS] = 100) among those with eGFRcr of >60 ml/min/1.73 m^2, to 9% (NNS = 11) in the eGFRcr 45–60 ml/min/1.73 m^2 group, and 40% (NNS = 3) in the eGFRcr 30–45 ml/min/1.73 m^2 group.

Qualitatively similar results were noted when analyses were performed using the CKD-EPI equation to calculate eGFRcr, though fewer individuals were reclassified downward to an eGFRcys of <30 ml/min/1.73 m^2 or eGFRcys of 30–45 ml/min/1.73 m^2 (Supplemental Table S3). The percentage of patients reclassified to an eGFR of <30 ml/min/1.73 m^2 was 5% (NNS = 20) among those in the CKD-EPI eGFRcr 45–60 ml/min/1.37 m^2 group and 27% (NNS = 4) in the eGFR 30–45 ml/min/1.73 m^2 group.

Factors associated with change in category

Factors independently associated with a more severe eGFR category by eGFRcys vs. MDRD eGFRcr were risk factors for kidney disease: older age (aRR = 2.21 per decade, 95%CI 1.79–2.73), ACR > 30 mg/g (aRR = 1.81, 95%CI 1.20–2.73) and higher BMI (aRR = 1.04 per kg/m^2, 95%CI 1.01–1.08) (Table 4). We did not identify any factors that had statistically significant associations with

Table 3
Reclassification of eGFR categories from creatinine to cystatin C and impact on metformin eligibility using a threshold of 30 ml/min/1.73 m^2

eGFRcys	eGFRcr <30 ml/min/1.73 m2 "do not use" (n = 31)	eGFRcr 30–44 ml/min/1.73 m2 "caution" (n = 58)	eGFRcr 45–60 ml/min/1.73 m2 "first line (n = 93)	eGFRcr >60 ml/min/1.73 m2 "first line" (n = 368)
<30 "do not use"	28 (90%)	**23 (40%)**	**8 (9%)**	**1 (1%)**
30–44 "caution"	**3 (10%)**	31 (53%)	**38 (41%)**	**32 (9%)**
45–60 "first line"	0	**4 (7%)**	35 (38%)	76 (21%)
>60 "first line"	0	0	12 (13%)	259 (70%)

Dark shading represents downward reclassified into "do not use" category; medium shading represents downward reclassification into "use with caution" category; light shading represents upward reclassification.

a less severe eGFR category by eGFRcys vs. MDRD eGFRcr. Results were similar when using CKD-EPI to calculate eGFRcr (Supplemental Table S4), although cardiovascular disease was a significant risk factor and albuminuria was not.

Discussion

The benefits of metformin for treatment of diabetes mellitus have long been appreciated. Since 1998, it has been considered the first-line agent for treatment of diabetes for individuals with preserved renal function. Newer statements released by diabetes and nephrology societies suggest using metformin as a first-line agent among individuals with mild kidney disease as well, defined by an eGFR of ≥45 ml/min/1.73 m^2. However, a black box warning recommending against metformin use among individuals with CKD defined by a serum creatinine threshold still exists in the United States [7,24]. Given these somewhat contrasting recommendations, we found that the strongest predictor of metformin avoidance in one adult Veterans Administration medical practice was severity of kidney function, defined by either serum creatinine or eGFRcr. Older age, lower glycosylated hemoglobin and congestive heart failure were also associated with decreased metformin use, but to a lesser extent. Because a variety of factors may confound eGFRcr and contribute to metformin's underuse, we tested the effect of eGFRcys on eGFR classification and metformin eligibility. Surprisingly, we found that eGFRcys more frequently moved patients into worse eGFR categories, resulting in decreased metformin eligibility.

The risk and benefit tradeoffs of metformin use among patients with diabetes and CKD support the use of a second measure of kidney function to improve eGFR classification and safe metformin use. On the one hand, diabetic adults with CKD may particularly benefit from metformin relative to other oral diabetes agents, as recent studies have suggested a lower risk of stroke, hospitalization for acute myocardial infarction, eGFR decline or development of ESRD, and death, among individuals who initiate diabetes therapy with metformin compared to a sulfonylurea [2,3]. Additionally, metformin is associated with fewer hypoglycemic events compared to other oral diabetes agents [25]. CKD independently predisposes to hypoglycemia via decreased gluconeogenesis and abnormal insulin metabolism [26]. This is also an important consideration for older adults with diabetes, as hospital admission rates for hypoglycemia in this population, often associated with falls [27], now exceed those for hyperglycemia [28]. On the other hand, risk of lactic acidosis among patients using metformin with severely impaired kidney function is real, though relatively rare [6].

Cystatin C has been recommended as a confirmatory test to diagnose CKD among individuals in whom creatinine-based eGFR measurements may not be accurate [16,28]. Compared to creatinine-based estimates of kidney function, cystatin C-based estimates are more highly correlated with eGFR decline among patients with diabetes [29]. Cystatin C may thus be useful to identify individuals at higher risk of metformin accumulation and lactic acidosis, potentially leading to safer prescribing practices. In our study, cystatin C reclassified 21% of individuals into different clinical eGFR categories compared to MDRD eGFRcr. Most patients were reclassified downward into a more severe eGFR categories. The number of patients needed to screen with cystatin C to reclassify an individual to <30 ml/min/1.73 m^2 (not eligible for metformin) was 11 among those with an MDRD eGFRcr of 45–60 ml/min/1.73 m^2 and approximately 3 among those with MDRD eGFRcr of 30–45 ml/min/1.73 m^2. While the overall degree of reclassification by cystatin C was consistent with prior studies, its predominantly uni-directional nature, with many more patients reclassified into a more severe eGFRcys category compared to eGFRcr, was surprising [30]. This finding may be driven by the lower muscle mass among patients with diabetes, which is not accounted for in either the MDRD or the CKD-EPI GFR estimating equations but is independent of eGFRcys [15]. The insensitivity of eGFRcr may be of most clinical importance among older patients, those who are obese, have albuminuria, or have an eGFRcr of <60 ml/min/1.73 m^2, as these were independent predictors of more severe cystatin C-based eGFR clinical categories in our study.

The ideal method to estimate kidney function remains an area of active research, as all kidney function estimation formulas have shortcomings when compared to the gold standard of measured GFR using urinary or plasma clearance of exogenous filtration markers [31]. Given its cost, imprecision, and measurement challenges, the role of measured GFR in clinical practice is also uncertain. Our study protocol, which compared cystatin C and serum creatinine-based estimates of GFR in a consecutive sample of adult Veterans with diabetes in primary care, mirrored a clinical setting. The strategy of ordering a confirmatory cystatin C for safe and enhanced prescribing of metformin is highly applicable to a variety of clinical settings. We did not compare creatinine-based estimates of GFR with estimates based on the combined creatinine–cystatin equation, as we were unaware of clinical laboratories that are reporting eGFR using the combined equation. However, because the combined equation approximates the average of eGFRcr and eGFRcys, it may be the ideal, single estimating equation for clinical use. This was a single center study with Veterans who were primarily older and male. Results cannot necessarily be extrapolated to other populations, although our study population was ethnically diverse and cystatin C has been shown to reclassify eGFR categories across diverse research patient populations [30].

In conclusion, we confirm low metformin use among individuals with mild kidney disease. Educational campaigns that highlight the recent recommendations for metformin eligibility may be helpful to enhance its use among individuals with preserved kidney function, while a clinical trial is needed to determine the risks and benefits of metformin use among individuals with eGFR of 30–44 ml/min/1.73 m^2. Given the degree of reclassification of clinical eGFR categories with cystatin C compared to creatinine, particularly for older diabetic adults with obesity, albuminuria, and/or eGFR of <60 ml/min/1.73 m^2, a strategy of reflexively measuring cystatin C in these populations before prescription (and possibly yearly) may also be helpful for clinicians. A second eGFR measurement with cystatin C may lead to less metformin use among individuals with an eGFRcr of <45 ml/min/1.73 m^2 due to downward reclassification. But, confirmation of eGFR of ≥45 ml/min/1.73 m^2 with cystatin C may result in greater clinician confidence to use metformin for this more sizeable population. A prospective study examining the risks/benefits of such a strategy on clinician prescribing practices and patient-level adverse events is needed to elucidate the role of cystatin C for metformin prescribing purposes.

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Conflict of interest

The authors declare they have no conflicts of interest.

Authorship

Drs. Delphine Tuot and Michael Shlipak are guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. DT obtained funding and contributed to study concept/design, acquisition of data, and drafting the manuscript. RS performed data analysis and critically revised the manuscript. HL contributed to data acquisition and reviewed the manuscript. CG reviewed/edited the manuscript. AH reviewed/edited the manuscript. MS contributed to study design, data interpretation and revision of the manuscript and provided study supervision.

Results in this manuscript were presented in poster format at the American Society of Nephrology Kidney Week meeting in Philadelphia, PA, on November 15, 2014.

Appendix. Supplementary material

Supplementary data to this article can be found online at doi:10.1016/j.jcte.2015.10.002.

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